REMARKS

Entry of this amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Claims 1-31, 37-38, 40-42, 44-50, and 52-65 are cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuation applications.

Claims 32-36, 39, 43, and 51 are currently amended. Claim 32 is amended to independent form and recites a method of exposing a cell that overexpresses ErbB2 to a first antibody that binds SEQ ID NO:2 of ErbB2 and subsequently exposing the cell to a second antibody that binds ErbB2 at an epitope other than SEQ ID NO:2. Claims 33-36, 39, 43, and 51 are amended to change dependency to claim 32. Support for these amendments can be found, for example, in Examples 3-4 and Figures 16-17.

Accordingly, after entry of this Amendment, claims 32-36, 39, 43, and 51 are pending.

Applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of the claims.

Examiner Interview

Applicants thank the Examiner for his time in discussing the amended, antibody combination claims presented herein with Applicants' representatives, Denise Kettelberger and Brian Dorn, on November 5, 2007. This reply is submitted in keeping with the comments and discussion of the interview.

Rejections under 35 U.S.C. § 102(b) and § 103(a)

The Examiner rejects claims 28-31, 37-38, 40, and 56-57 under 35 U.S.C. § 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over either Shepard et al. (*J. Clin. Immunol.*, 1991) or Lewis et al. (*Cancer Immunol. Immunother.*, 1993). The Examiner rejects claims 28-40 and 42-65 for reasons of record that date back to the Office Action of July 10, 2000. Applicants respectfully traverse these rejections.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." *Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *See also*, MPEP

§2131. To establish a *prima facie* case of obviousness, the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicants respectfully assert that the cited art does not teach each and every claim element, specifically where antibody binding induces apoptosis. The claims have been amended to recite a method of exposing ErbB2 overexpressing cells to a first and a second antibody. Although both Shepard and Lewis disclose multiple anti-ErbB2 antibodies, neither reference discloses use of the recited first and second antibodies in a combination treatment. Each of the anti-ErbB2 antibody characterization studies performed by Shepard and by Lewis tested the application of a single antibody to a culture of cells. Lewis and Shepard fail to disclose or even suggest, using a combination of the antibodies as claimed. For at least this reason, the Examiner has not established anticipation or a *prima facie* case of obviousness.

Unexpected Success. Applicants respectfully assert the combination of a first antibody that binds SEQ ID NO:2 of ErbB2 and a second antibody that binds ErbB2 at an epitope other than SEQ ID NO:2 provides an enhanced inhibitory effect on cells that overexpress ErbB2 (See, for example, Examples 3-4 and Figure 17).

> A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue. *In re Corkill*, 771 F.2d 1496, 1501 (Fed. Cir. 1995); MPEP 716.02(a)

Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the separate effects. *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989); MPEP 716.02(a). Applicants have shown that the combination of antibodies 4D5 and 7C2 or 4D5 and 7F3 have enhanced cytotoxic effects (see Example 3 and Figure 16).

> Treatment of BT474 breast tumor cells with 0.5 μg/ml MAb 7C2 followed by 10 μg/ml MAb 4D5 results in a reduction in a viable (annexin V negative/PI negative) cells to 12%, compared to 68% or 29.1% with MAb 4D5 or 7C2 alone, respectively. This additive effect is also seen with a suboptimal dose of MAb 7C2, where treatment with 0.25 μg/ml 7C2 plus 10 μg/ml 4D5 lead to a decrease in viable cells to 37.5%, compared to 68% for MAb 4D5 alone and 77% for 7C2 alone. Specification at p. 58, lines 1-10.

In addition, the potentiated effect occurs early and throughout the duration of administration (page 59, lines 22-29 and Figure 17). The apoptotic antibodies (7C2 and 7F3) alone produced a

growth inhibitory effect early that was lost over time. Antibody 4D5 produced a growth inhibitory effect throughout the study. The combination of antibodies (4D5 with either 7F3 or 7C2) produced an enhanced inhibitory effect early and throughout the duration of the time points. For at least these reasons, unexpected results arising from the combination of an antibody binding SEQ ID NO:2 of ErbB2 and an antibody that binds an ErbB2 epitope other than SEQ ID NO:2 have been demonstrated.

Applicants respectfully assert the Examiner has not established anticipation or a *prima facie* case of obviousness. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) and § 103(a).

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects claims 32-36, 39, 42-45, 49-55, 59 and 61-62 under 35 U.S.C. § 103(a) as allegedly obvious over either Shepard et al. (*J. Clin. Immunol.*, 1991) or Lewis et al. (*Cancer Immunol. Immunother.*, 1993) in view of Fendly et al. (*Cancer Res.*, 1990), Deshane et al. (*J. Invest. Med.*, 1995) and Senter et al. (U.S. Patent No. 4,975,278). Applicants respectfully traverse this rejection.

As discussed above, neither Shepard nor Lewis disclose a combination of anti-ErbB2 antibodies to inhibit cell growth nor enhanced effects of such a combination. Applicants respectfully assert that Fendly, Deshane, and Senter do not remedy the deficiencies of Shepard and/or Lewis. As the Examiner has characterized the three additional references, these references do not disclose or suggest a combination of anti-ErbB2 antibodies to inhibit cell growth nor disclose the enhanced effects of such a combination. Fendly is cited for disclosing production and further characterization of antibodies 7C2 and 7F3. Senter discloses a system for delivery of cytotoxic drugs. Deshane discloses a gene therapy treatment model. Applicants assert that these references do not teach or suggest the instantly claimed method.

Applicants assert that Deshane does not teach an antibody that binds its epitope and thereby triggers apoptosis. The cited Deshane reference is an abstract presented at a scientific conference, and is limited in its disclosure. Subsequent publications by the same authors present a further description of the gene therapy treatment model and characterization of the antibody used in the study. DeShane's method and same antibody (an sFv) is disclosed in further detail in

U.S. Patent No. 5,910,486 and DeShane et al., *Gene Therapy* 1:332-7 (1994). DeShane's sFv that induces apoptosis is the construct pGT21.

The '486 patent discloses transfection of two constructs (pGT20 and pGT21) into SKOV3 cells (See, Example 6 at col. 21-22). Both constructs encode the same anti-ErbB2 sFV. The only difference between pGT20 and pGT21 is a signal sequence directing pGT21 to the endoplasmic reticulum (col. 16, lines 29-33) which is lacking in pGT20.

Transfection of pGT20 (no signal sequence) did not affect cell number, whereas transfection of pGT21 (ER signal sequence) caused a decrease in cell viability (see col. 21-22 and Figure 7). Subsequent tests confirmed that apoptosis occurred (col. 22, lines 11-50)in the pGT21 samples. In Deshane's system, the signal sequence is key to causing apoptosis, and not the intracellular antibody. It appears the apoptotic effect is specifically mediated by the antibody in the specific compartment of the endoplasmic reticulum. In view of the foregoing, Applicants assert that Deshane does not disclose or suggest an anti-ErbB2 antibody capable of binding an epitope at the cell surface and thereby triggering apoptosis.

For at least these reasons, Applicants respectfully assert the cited references do not disclose or suggest the claimed method of exposing a cell overexpressing ErbB2 to a first antibody that binds SEQ ID NO:2 of ErbB2 and a second antibody that binds an epitope of ErbB2 other than SEQ ID NO:2. Further, none of the cited references disclose an anti-ErbB2 antibody that triggers apoptosis by binding SEQ ID No:2. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 42-45, 59, 61, and 62 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Caims 42, 44-45, 59, and 61-62 are cancelled. Claim 43 is amended to depend from claim 32. These amendments render the rejection moot, and Applicants respectfully request its removal.

Summary

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: November 26, 2007

Denise M. Kettelberger
Reg. No. 33,924
DMK:BRD:lek